

Claims

1. A mutein of a bone morphogenetic protein, whereby the mutein comprises an amino acid substitution compared to the wildtype of the bone morphogenetic protein at the amino acid position corresponding to amino acid position 51 of human BMP-2.
2. The mutein according to claim 1, whereby the amino acid at the position corresponding to amino acid position 51 of human BMP-2 is leucine in the wildtype form of the bone morphogenetic protein and is preferably proline in the mutein.
3. The mutein according to claim 1 and 2, whereby the bone morphogenetic protein is selected from the group comprising hBMP-2, hBMP-4, hBMP-5, hBMP-6, hBMP-7, hBMP-8, hGDF-5, mGDF-6, mGDF-7, hBMP-10 and hGDF-2.
4. The mutein according to any of claims 1 to 3, whereby
  - the bone morphogenetic protein is hBMP-2 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 51;
  - the bone morphogenetic protein is hBMP-4 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 53;
  - the bone morphogenetic protein is hBMP-5 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 68;
  - the bone morphogenetic protein is hBMP-6 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 68;
  - the bone morphogenetic protein is hBMP-7 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 75;
  - the bone morphogenetic protein is hBMP-8 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 75;

- the bone morphogenetic protein is hGDF-5 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 56;
  - the bone morphogenetic protein is mGDF-6 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 56;
  - the bone morphogenetic protein is mGDF-7 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 82;
  - the bone morphogenetic protein is hBMP-10 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 44; and
  - the bone morphogenetic protein is hGDF-2 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 45.
5. The mutein according to any of claims 1 to 4, wherein the wildtype of
- hBMP-2 comprises an amino acid sequence according to SEQ ID No. 1;
  - hBMP-4 comprises an amino acid sequence according to SEQ ID No. 3;
  - hBMP-5 comprises an amino acid sequence according to SEQ ID No. 5;
  - hBMP-6 comprises an amino acid sequence according to SEQ ID No. 7;
  - hBMP-7 comprises an amino acid sequence according to SEQ ID No. 9;
  - hBMP-8 comprises an amino acid sequence according to SEQ ID No. 11;
  - hGDF-5 comprises an amino acid sequence according to SEQ ID No. 13;
  - mGDF-6 comprises an amino acid sequence according to SEQ ID No. 15;

- mGDF-7 comprises an amino acid sequence according to SEQ ID No. 17;
- hBMP-10 comprises an amino acid sequence according to SEQ ID No. 19; and
- hGDF-2 comprises an amino acid sequence according to SEQ ID No. 21.

6. The mutein according to claim 5, whereby the wildtype of

- hBMP-2 is encoded by a nucleic acid according to SEQ ID No. 2;
- hBMP-4 is encoded by a nucleic acid according to SEQ ID No. 4;
- hBMP-5 is encoded by a nucleic acid according to SEQ ID No. 6;
- hBMP-6 is encoded by a nucleic acid according to SEQ ID No. 8;
- hBMP-7 is encoded by a nucleic acid according to SEQ ID No. 10;
- hBMP-8 is encoded by a nucleic acid according to SEQ ID No. 12;
- hGDF-5 is encoded by a nucleic acid according to SEQ ID No. 14;
- mGDF-6 is encoded by a nucleic acid according to SEQ ID No. 16;
- mGDF-7 is encoded by a nucleic acid according to SEQ ID No. 18;
- hBMP-10 is encoded by a nucleic acid according to SEQ ID No. 20; and
- hGDF-2 is encoded by a nucleic acid according to SEQ ID No. 22.

7. A bone morphogenetic mutein, whereby the mutein is not binding to a first bone morphogenetic protein receptor and the mutein is binding to at least a modulator protein,

whereby the modulator protein is selected from the group comprising the noggin protein family, the DAN protein family, the chordin protein family and the cysteine-knot-containing BMP modulator proteins.

8. A bone morphogenetic mutein, preferably according to claim 1, comprising a pre-helix loop structure which interacts with a second bone morphogenetic protein receptor.

9. The bone morphogenetic mutein according to claim 7 and 8, whereby the first and/or the second bone morphogenetic protein receptor is BR1A or BR1B.

10. The bone morphogenetic mutein according to claim 8 and 9, whereby the interaction is related to an amino acid residue, preferably amino acid residue Gln86 of BR1A or Gln 67 of BR1B.

11. A bone morphogenetic mutein, preferably according to any of claims 6 to 10, comprising a pre-helix loop structure having an interaction with a second bone morphogenetic protein receptor, whereby the interaction of the pre-helix loop structure of the bone morphogenetic mutein with the second bone morphogenetic protein receptor is different from the interaction of the pre-helix loop structure of the wildtype bone morphogenetic protein with the second bone morphogenetic protein receptor.

12. The bone morphogenetic mutein according to any of claims 8 to 11, whereby the different interaction or the change is represented in refraction data, preferably such refraction data being acquired at room temperature to a resolution of at least about 2.7 Å.

13. The bone morphogenetic mutein according to any of claims 7 to 12, whereby the pre-helix loop structure is mutated compared to the wildtype of the bone morphogenetic protein.

14. The bone morphogenetic mutein according to claim 13, whereby the amino acid corresponding to leucine at position 51 of the wildtype BMP-2 is mutated.

15. The bone morphogenetic mutein according to claim 13 or 14, whereby the amino acid corresponding to leucine at position 51 of human BMP-2 is mutated to proline.

16. The bone morphogenetic mutein according to any of claims 7 to 15, whereby the bone morphogenetic mutein is a mutein of a bone morphogenetic protein selected from the group comprising hBMP-2, hBMP-4, hBMP-5, hBMP-6, hBMP-7, hBMP-8, hGDF-5, mGDF-6, mGDF-7, hBMP-10 and hGDF-2.
17. The bone morphogenetic mutein according to claim 16, whereby the bone morphogenetic protein is BMP-2 or pro-BMP-2.
18. A bone morphogenetic protein comprising an amino acid sequence according to any of SEQ ID Nos. 23 to 33.
19. The bone morphogenetic mutein according to claim 18, whereby the bone morphogenetic mutein is a bone morphogenetic mutein according to any of claims 7 to 18.
20. A nucleic acid coding for a bone morphogenetic mutein according to any of claims 1 to 19 and/or a complementary strand thereto.
21. A nucleic acid comprising a nucleic acid sequence according to SEQ ID Nos. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22, preferably coding for a bone morphogenetic mutein according to any of claims 1 to 19, and/or a complementary strand thereto.
22. A nucleic acid coding for a bone morphogenetic mutein according to any of claims 1 to 19, whereby the nucleic acid would hybridize to the nucleic acid according to claim 20 or 21 but for the degeneracy of the genetic code, more preferably under stringent conditions.
23. A vector comprising a nucleic acid according to any of claims 20 to 22, whereby the vector is preferably an expression vector.
24. A cell, preferably a mammalian cell, comprising a nucleic acid according to any of claims 20 to 22 and/or a vector according to claim 23.

25. A host organism, preferably a mammalian host organism and more preferably a non-human host organism comprising a cell according to claim 24.
26. A method for the production of a bone morphogenetic mutein according to any of claims 1 to 19, comprising the steps of
- a) cultivating a cell according to claim 25 in a cultivation broth and
  - b) preparing the bone morphogenetic mutein from the cell and/or from the cultivation broth.
27. A monoclonal antibody specifically binding to a bone morphogenetic mutein according to any of claims 1 to 19.
28. A composition comprising a mutein according to any of claims 1 to 19 and/or a nucleic acid according to any of claims 20 to 22.
29. A pharmaceutical composition comprising a mutein according to any of claims 1 to 19 or a nucleic acid according to any of claims 20 to 22, and a pharmaceutically acceptable carrier.
30. Use of a bone morphogenetic mutein according to any of claims 1 to 19 and/or of a nucleic acid according to any of claims 20 to 22, for the manufacture of a medicament.
31. Use according to claim 30, wherein the medicament is for the treatment and/or prevention of a disease selected from the group comprising fibrotic diseases, wound healing, hypervascularization, vascular diseases, fractures, and osteoporosis.
32. The use according to claim 31, whereby the fibrotic disease is selected from the group comprising renal fibrosis, hepatic cirrhosis, pulmonary fibrosis and chronic inflammation, preferably chronic inflammation associated with asthma.
33. The use according to claim 31, wherein the wound healing is related to keloid, cicatrization, and peritoneal obliteration.

34. The use according to claim 31, whereby the hypervascularization is related to or associated with retinopathies, arteriosclerosis and/or tumors.
35. Use according to claim 31, whereby the fractures are non-healing fractures.
36. The use according to claim 31, whereby the disease is osteoporosis.
37. Use of a morphogenetic mutein according to any of claims 1 to 19 as inhibitor to a BMP interacting protein.
38. The use according to claim 37, wherein the BMP interacting protein is selected from the group comprising the noggin protein family, the DAN protein family and the chordin protein family.